2. (Amended) A topical composition as claimed in claim 1, wherein the compound that promotes the synthesis of nerve growth factor is selected from the group consisting of: vitamin D_3; a vitamin D_3 derivative 1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene, and other vitamin D_3 derivatives which promote the synthesis of nerve growth factor, pharmaceutically acceptable salts thereof and mixtures thereof.

6. (Amended) A composition as claimed in claim 1, wherein the antioxidant comprises at least one compound selected from the group consisting of: ascorbyl palmitate, ascorbic acid, vitamin A, vitamin E acetate, an α-lipoic acid, coenzyme Q10, glutathione, catechin, galangin, rutin, luteolin, morin, fisetin, silymarin, apigenin, gingkolides, hesperitin, cyanidin, citrin, derivatives thereof which exhibit antioxidant activity, and pharmaceutically acceptable salts thereof.

REMARKS

This Amendment is responsive to the Office Action dated July 18, 2001. Claims 1 and 6 have been amended. Claims 1-25 are currently pending in the present application.

Restriction Requirement

The Examiner has required restriction between the claims of Group I (claims 1-15), drawn as to a composition for the treatment of diabetic neuropathy, and Group II (claims 16-25), drawn as to a method for the treatment of diabetic neuropathy. Applicant provisionally elects Group I, claims 1-15, for further prosecution with traverse.

The Examiner gives, as a reason for the restriction, that the process, as claimed can be practiced with another materially different product. In support of this reason, the Examiner alleges that the process, as claimed, can be practiced with a formulation including a prostaglandin I derivative and an anti-diabetic agent. However, the process as claimed, requires

administration of an amount of a compound, which is effective to promote the synthesis of nerve growth factor, an amount of an aldose reductase inhibitor effective to inhibit aldose reductase and an effective amount of an antioxidant. Thus, the process, as claimed, requires the use of the product of claim 1. Therefore, the Examiner's position that the process, as claimed, can be practiced with a materially different product than the product of claim 1 is clearly incorrect. Favorable consideration and withdrawal of the restriction on this basis is requested.

According to the Examiner, Group I contains multiple species. One of the species is a combination of the aldose reductase inhibitor being quercetin and the antioxidant being ascorbyl palmitate. Applicant provisionally elects the species containing quercetin and ascorbyl palmitate, with traverse. Claims 1-6, 10, 12-13 and 15 read on the elected species. Claim 1 is generic. Applicant traverses the election of species requirement on the basis that it does not represent an undue burden to the examiner to examine all of the claimed species together in a single application.

Objections

The Examiner has objected to the usage of parenthetical expression "(Vitamin C)" in claim 6. "(Vitamin C)" has been deleted from claim 6. Since Vitamin C is ascorbic acid and ascorbic acid is already present in claim 6, no new matter has been added. The original purpose of the parenthetical expression, "(Vitamin C)" was to give the alternative name of ascorbic acid in the claim. Two minor spelling errors in claim 6 were also corrected.

35 U.S.C. §112 rejections

Claims 1, 2, 6 and 7 have been rejected under 35 U.S.C. 112, first paragraph for not enabling a person skilled in art use "other vitamin D_3 derivatives which promote the synthesis of nerve growth factor." This rejection is respectfully traversed and reconsideration is requested for the reasons, which follow.

"A compound or a derivative which promotes the synthesis of nerve growth factor" by itself should enable a person skilled in art to use this invention for the following reasons.

The art of nerve growth factor (NGF) synthesis is well established within the domestic and international medical research communities. Understanding the role of NGF is critical to the treatment of degenerative nerve diseases such as Alzheimer's disease, Parkinson's disease, and diabetes. To that extent, many researchers have sought to stimulate or repress NGF either by genetic manipulation or by the synthesis of pharmaceutical compounds. This research has lead to the discovery of compounds, which promote NGF synthesis such as idebenone and propentofylline[1], interleukin-1[2], leteprinim potassium[3], and the vitamin D_3 derivative CB1093[4]. Published information about these compounds and others are readily available to a person skilled in the art. Therefore, a person skilled in art knows numerous compounds that promote the synthesis of nerve growth factor including at least one derivative of vitamin D_3.

From the article by Ruiz, it is clear that a skilled person is capable of synthesizing vitamin D_3 derivatives, of identifying that such compounds are vitamin D_3 derivatives, and of determining whether such compounds promote the synthesis of nerve growth factor. In fact, a

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[1] K. Yamada, et. al., *Orally Active NGF Synthesis Stimulators: Potential Therapeutic Agents in Alzheimer's Disease*, BEHAVIOR BRAIN RESEARCH, 83(1-2):117-22 (Feb. 1997).
[2] Rueff, A. and Mendell, L., *Nerve Growth Factor and Inflammatory Pain*, IASP Newsletter, January/February 1996).
[3] Press Release Article on NEOTROPHIN (TM), http://www.neotherapeutics.com/r980727.html (July 27, 1998)
[4] Riaz, S., *Vitamin D3 Derivative (CB1093) Induces Nerve Growth Factor and Prevents Deutotrophic Defects in Streptozotocin-diabetic Rats*. DIABETOLOGIA 42: 1308-1313 (1999).

skilled person can use a simple test on rats to determine whether a particular vitamin D_3 derivative promotes the synthesis of nerve growth factor as is detailed in the articles cited above. Accordingly, the skilled person is perfectly capable of making and identifying vitamin D_3 derivatives, which promote synthesis of nerve growth factor. The present specification clearly teaches a skilled person how to use such D_3 derivatives and thus the requirements of 35 U.S.C. §112 with regard to enablement, have been met.

In addition, "derivative" is further clearly defined at lines 21-24 of page 4 as "compounds, which possess at least one structural moiety in common with the compound for which they are derived, which common structure is a characterizing structural element of the compound from which the derivative is derived." In addition, at least one derivative of vitamin D_3 is illustrated at lines 17-18 of page 4 of the specification, namely, "1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene."

For the forgoing reasons, Applicant respectfully submits that the scope of claim 1 is commensurate with enabled disclosure in the specification. Since claims 2, 6 and 7 all depend from claim 1 and claims 2, 6 and 7 all have narrower scope than claim 1, the scope of claims 2, 6 and 7 are enabled by the specification for the same reasons as given for claim 1. Favorable consideration and withdrawal of the rejection is respectfully requested.

Claims 1-15 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is respectfully traversed and reconsideration is requested for the reasons, which follow.

The Examiner rejected claim 1 on the basis that the term, "the compositions" in line 3 lacked antecedent basis in the claim. Claim 1 has been amended to recite a singular "composition" in all of its occurrences to obviate this rejection.

Claim 2 has been rejected because the Examiner averred that "vitamin D_3" was a narrower range within a broader range "other vitamin D_3 derivatives..." Ex parte Wu, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989) does not apply here. First of all, vitamin D_3 is not a vitamin D_3 derivative. According to "Webster's Ninth New Collegiate Dictionary," "derivative" means "a chemical substance related structurally to another substance and theoretically derivable from it (emphasis added)." The derivative is different from the substance it derived from. Therefore, "vitamin D_3" is not within the scope of "vitamin D_3 derivatives." In fact, there is overlap at all. Therefore, claim 2 does not have a narrower range with a broader range. In order to further clarify this point, claim 2 has been amended to insert "a vitamin D_3 derivative" before the specifically claimed vitamin D_3 derivative in claim 2. In addition, the word, "other" makes it clear that "other vitamin D_3 derivatives" refers to vitamin D_3 derivatives other than the vitamin D_3 derivative that is specifically claimed in claim 2. Favorable consideration and withdrawal of the objection in view of this amendment is requested.

The same reasoning applies to the rejection of claims 3-15, since this rejection was based on the fact that these claims depend from claims 1-2. Favorable consideration and withdrawal of the rejections is respectfully requested.

35 U.S.C. § 102(b) Rejection

Claims 1-6, 10, 12-13, and 15 were rejected under 35 U.S.C. § 102(b) as being anticipated by Riley (U.S. patent no. 5,976,568). This rejection is respectfully traversed and reconsideration is requested for the reasons, which follow.

Amended claim 1 of the present application requires "an amount of a compound that promotes synthesis of nerve growth factor which is effective when administered in the

composition to promote synthesis of nerve growth factor." Amended claim 1 further requires "an amount of an aldose reductase inhibitor which is effective when administered in the composition to inhibit aldose reductase." Amended claim 1 further requires "an effective amount of an antioxidant."

For the compound to effectively promote nerve growth factor synthesis, it has to be administered in an effective dosage such as 6-14.3 IU per Kg of body weight (see lines 26-27 of page 4). For the aldose reductase inhibitor to be effective, it has to be administered in an effective dosage such as 13-21.4 mg/Kg body weight (see lines 25-26 of page 6). In addition, when the antioxidant is ascorbyl palmitate, the effective amount of ascorbyl palmitate is 11-28.6 mg/Kg body weight of the patient per day (see lines 22-23 of page 7). Therefore, in order to satisfy the requirements of amended claim 1 of the present application, the compound promoting the nerve growth factor synthesis such as vitamin D3, the aldose reductase inhibitor such as quercetin and the antioxidant such as ascorbyl palmitate must be mixed at proper ratios in the composition in order to for them both to fall within their own effective ranges when being administered in the composition. Even if we take the extreme end points of the above dosage ranges, we can conclude the amended claim 1 requires that ratio for vitamin D3 to quercetin be within 0.28 IU/mg~1.1 IU/mg; the ratio for vitamin D3 to ascorbyl palmitate be within 0.21 IU/mg ~ 1.3 IU/mg; and the ratio for qucertin to ascorbyl palmitate be within 0.45 ~ 1.95.

The examiner averred that US. Patent No. 5,976,568 to Riley anticipates claim 1 of the present application. In contrast, table II (cols. 25~26) of Riley, which the Examiner cited as an example anticipating claim 1 of the present application, does not disclose a composition containing all of the three components in one composition as required by claim 1 at all. In fact, modules 1 and 2 in table II include only vitamin D_3 and ascorbyl palmitate without including

quercetin. Module 3 in table II includes only ascorbyl palmitate and quercetin without including vitamin D_3. Amended claim 1 requires that all the three components be included in the composition at same time. Therefore, table II of Riley does not anticipate amended claim 1 of the present application.

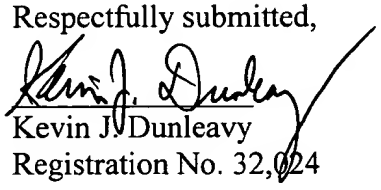
In addition, claim 1 of Riley, which was cited by the Examiner as another example anticipating claim 1 of the present application, does not disclose a composition meets all the requirements of amended claim 1 of the present application. Claim 1 of Riley lists a daily oral dosage and not a composition. As is clear from a reading of the specification of Riley, a daily oral dosage is not the same as a composition. Rather, a daily oral dosage is made up of several individual modules. Each module is a composition as shown in Tables II-III. Thus, for example, the daily oral dosage referred to in claim 1 is taught by Riley to be administered as a combination of several different modules, i.e. modules 1-3. Therefore, the daily oral dosage of claim 1 does not exist as a single composition nor does Riley teach or suggest that it can or should be formulated as a single composition. Accordingly, claim 1 does not anticipate the elected species of the present invention. Favorable consideration and withdrawal of the rejection is requested.

Moreover, Riley teaches away from administration of the daily oral dosage as a single composition since the entire purpose of Riley is to provide additional nutritional, dietary and health benefits by providing the compositions in the form of specific modules. Accordingly, the elected species is also not obvious over the disclosure of Riley since Riley teaches away from combining the three ingredients of the elected species into a single composition. The same arguments apply to claim 2 of Riley. None of the remaining claims of Riley contain all three ingredients of the elected species.

All references cited in this response in support of the applicant's arguments have been attached herewith for the Examiner's convenience.

In view of the foregoing remarks, Applicant respectfully submits that all of the pending claims are in condition for allowance and respectfully requests a favorable Office Action so indicating.

Respectfully submitted,



Kevin J. Dunleavy
Registration No. 32,024

Dated: October 18, 2001

KNOBLE & YOSHIDA, LLC
Customer No. 21,302
Eight Penn Center, Suite 1350
1628 John F. Kennedy Blvd.
Philadelphia, PA 19103
(215) 599-0600

MARKED UP COPY OF THE AMENDED CLAIMS

1. (Amended) A composition for the treatment of diabetic neuropathy by a method of administration selected from the group consisting of oral administration, parenteral administration and inhalation, the compositions comprising a mixture of an amount of a compound that promotes synthesis of nerve growth factor which is effective when administered in the composition to promote synthesis of nerve growth factor, an amount of an aldose reductase inhibitor which is effective when administered in the composition to inhibit aldose reductase and an effective amount of an antioxidant.

2. (Amended) A topical composition as claimed in claim 1, wherein the compound that promotes the synthesis of nerve growth factor is selected from the group consisting of: vitamin D_3~~,~~; a vitamin D_3 derivative 1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene, and other vitamin D_3 derivatives which promote the synthesis of nerve growth factor, pharmaceutically acceptable salts thereof and mixtures thereof.

6. (Amended) A topical composition as claimed in claim 1, wherein the antioxidant comprises at least one compound selected from the group consisting of: ascorbyl palmitate, ascorbic acid ~~(vitamin C)~~, vitamin A, vitamin E acetate, an α-lipoic acid, ~~especially DL- α-lipoic acid,~~ coenzyme Q10, glutathione, catechin, galangin, rutin, luteolin, morin, fisetin, ~~silymerin~~silymarin, apigenin, gingkolides, hesperitin, cyanidin, citrin, derivatives thereof which exhibit antioxidant activity, and pharmaceutically acceptable salts thereof.